

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 45/06, 31/445, 31/415 // (A61K 31/445, 31/415, 31/40)	A1	(11) International Publication Number: WO 92/00103 (43) International Publication Date: 9 January 1992 (09.01.92)												
(21) International Application Number: PCT/GB91/00992 (22) International Filing Date: 20 June 1991 (20.06.91) (30) Priority data: <table border="0" style="width: 100%;"><tr><td style="width: 30%;">9014354.6</td><td style="width: 30%;">28 June 1990 (28.06.90)</td><td style="width: 40%;">GB</td></tr><tr><td>9014364.5</td><td>28 June 1990 (28.06.90)</td><td>GB</td></tr><tr><td>9014365.2</td><td>28 June 1990 (28.06.90)</td><td>GB</td></tr><tr><td>9014367.8</td><td>28 June 1990 (28.06.90)</td><td>GB</td></tr></table> (71) Applicant (for all designated States except US): BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : JOHNSON, Edward, Stewart [GB/GB]; Willow Vale, Castle End Road, Ruscombe, Berkshire RG10 9XG (GB).		9014354.6	28 June 1990 (28.06.90)	GB	9014364.5	28 June 1990 (28.06.90)	GB	9014365.2	28 June 1990 (28.06.90)	GB	9014367.8	28 June 1990 (28.06.90)	GB	(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
9014354.6	28 June 1990 (28.06.90)	GB												
9014364.5	28 June 1990 (28.06.90)	GB												
9014365.2	28 June 1990 (28.06.90)	GB												
9014367.8	28 June 1990 (28.06.90)	GB												
(54) Title: PHARMACEUTICAL PREPARATIONS (57) Abstract A pharmaceutical product comprising two or three active ingredients as a combined preparation for simultaneous, separate or sequential use in therapy of depression and/or migraine.														

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

-1-

PHARMACEUTICAL PREPARATIONS

The present invention relates to pharmaceutical preparations having antidepressant and/or antimigraine activity.

5

It has now been found that a combination of two or three active agents having different mechanism of action with respect to 5-HT (5-hydroxytryptamine) has good antidepressant and/or antimigraine activity. The effectiveness of the combination is potentially greater than could be predicted from a consideration of the activities of the individual components and it appears that a synergistic effect is being produced.

10 Accordingly, the present invention provides a pharmaceutical product comprising two or three active ingredients selected from a 5-HT₃ receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT₁ receptor agonist, as a combined preparation for simultaneous, separate or sequential use in therapy of depression and/or migraine.

Suitable combinations are as follows:

- 5-HT₃ antagonist + 5-HT re-uptake inhibitor;
- 25 5-HT₃ antagonist + 5-HT₁ agonist;
- 5-HT₁ agonist + 5-HT re-uptake inhibitor; and
- 5-HT₃ antagonist + 5-HT re-uptake inhibitor + 5-HT₁ agonist.

Suitable examples of 5-HT₃ receptor antagonists are as described in WO 89/04660 and WO 90/01996 (Beecham Group p.l.c.), in particular BRL 43694A (granisetron) BRL 46470A (Example 5 in EP-A-247266); ondansetron or LY 277359.

Other examples of 5-HT₃ receptor antagonists are described 35 in EP-A-410509 (Duphar International Research B.V.), EP-A-

-2-

420086 (Fujisawa Pharmaceutical Co., Ltd.), EP-A-403261 (Glaxo Group Limited), EP-A-405784 (Ono Pharmaceutical Co., Ltd.), EP-A-419397 (A/S Ferrosan), EP-A-417746 (G.O. Searle & Co.) and EP-A-407137 (Yoshitomi Pharmaceutical Industries Ltd.).

Suitable examples of 5-HT re-uptake inhibitors include the antidepressants, paroxetine and femoxetine (U.S. Patent No. 4007196), citalopram, sertraline, fluoxetine, clomipramine, 10 fluvoxamine, cianopramine, ifoxetine, cericlamine, SL 810385 (Synthelabo) and seproxetine.

Suitable examples of 5-HT₁ receptor agonists include those compounds described in GB 2035310A; GB 2124210A; 15 EP-A-145459; GB 2150932; EP-A-147107; GB 2185020A; EP-A-303506; EP-A-303507; EP-A-354777; EP-A-254433; and GB 2162522A (Glaxo Group Limited) in particular the compound GR 43175 (sumatriptan) or GR 85548; and EP-A-313397 (The Wellcome Foundation Limited).

20

Information with respect to structure and activity of the specific compounds listed hereinbefore may be obtained from well known pharmaceutical industry references, such as "Pharmaprojects", PJB publications Limited, Richmond, 25 Surrey, U.K.

In a preferred aspect, the active components of the product are administered simultaneously although they may be administered separately e.g. the 5-HT₃ antagonist 30 administered first.

The present invention further provides a pharmaceutical composition comprising two or three active ingredients selected from a 5-HT₃ receptor antagonist, a 5-HT re-uptake 35 inhibitor and a 5-HT₁ receptor agonist in combination with a

-3-

pharmaceutically acceptable carrier.

The invention yet further provides the use of two or three active ingredients selected from a 5-HT₃ receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT₁ receptor agonist in the manufacture of a pharmaceutical preparation for simultaneous, separate or sequential use in depression and/or migraine therapy.

10 The product of the invention may be administered by the oral route to humans and may be compounded in the form of syrup, tablets or capsule for either separate, sequential or simultaneous administration.

15 However, they may be adapted for other modes of administration, for example parenteral administration. Other alternative modes of administration include sublingual or transdermal administration.

20 Generally, compositions containing from about 2.5 to 15 mg of granisetron or 0.01 to 10 mg of BRL 46470A, 10-50 mg of paroxetine and 10-50 mg sumatriptan in a ratio of around 1:4:4 are effective, but this will depend on the activity of the 5-HT₃ receptor antagonist, 5-HT re-uptake inhibitor
25 and/or 5-HT₁ agonist.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit-dose. Suitable unit dose forms include tablets,
30 capsules and powders in sachets or vials. Such unit dose forms may contain a total of from 0.01 to 100 mg of a 5-HT₃ receptor antagonist and more usually from 0.5 to 50 mg, for example 0.5 to 25 mg such as 0.5, 1, 2, 3, 5, 10, 15 or 20 mg. The unit dose form will normally contain from about 5
35 to 100 mg of the 5-HT re-uptake inhibitor and/or 5 to 100 mg of the 5-HT₁ agonist, more usually 10 to 50 mg, for example

-4-

10, 15, 20, 25, 30 mg. Such compositions may be administered from 1 to 6 times a day, more usually from 2 to 4 times a day, in a manner such that the daily dose of 5-HT₃ receptor antagonist is from 0.5 to 200 mg for a 70 kg human adult and more particularly from 0.5 to 25 mg, and the daily dose of the 5-HT re-uptake inhibitor and/or 5-HT₁ agonist, is from 10 to 500 mg for a 70 kg human adult and more particularly from 10 to 100 mg.

10 With the above indicated dosage range, no adverse toxicological effects are indicated with the composition of the invention.

The compositions of the invention may be formulated with 15 conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavouring agent. They are formulated in conventional manner, for example in a manner similar to that used for anti-hypertensive agents.

20 It is greatly preferred that the 5-HT₃ receptor antagonist, 5-HT re-uptake inhibitor and/or 5-HT₁ receptor agonist, are administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

25 Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions 30 or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually 35 presented in a unit dose, and contain conventional

-5-

excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

5

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycolate. Suitable lubricants
10 include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by
15 conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

20

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before
25 use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example
30 lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl
35 p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

-6-

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

5 For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the
10 compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be
15 frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the
20 vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

25

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

30 It will be appreciated that each component of the product of the invention may be administered by a different route.

The present invention yet further provides a method of treating depression and/or migraine in mammals including
35 man, which comprises administering to the suffering mammal an effective amount of a pharmaceutical composition

-7-

comprising two or three active ingredients selected from a 5-HT₃ receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT₁ receptor agonist, in combination with a pharmaceutically acceptable carrier.

5

Standard methods for assessing 5-HT₃ receptor antagonist activity, 5-HT₁ receptor agonist activity and 5-HT re-uptake inhibition activity are known in the art, and are, for example, described or referenced in the aforementioned
10 patent publication references.

Antidepressant and/or antimigraine activity is assessed in appropriate animal models for determining such activities and in appropriate clinical trial methods.

15

-8-

Claims

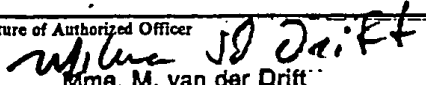
1. A pharmaceutical product comprising two or three active ingredients selected from a 5-HT₃ receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT₁ receptor agonist, as a combined preparation for simultaneous, separate or sequential use in therapy of depression and/or migraine.
2. A pharmaceutical product according to claim 1 comprising two active ingredients which are a 5-HT₃ receptor antagonist and a 5-HT re-uptake inhibitor.
3. A pharmaceutical product according to claim 1 comprising two active ingredients which are a 5-HT₃ receptor antagonist and a 5-HT₁ receptor agonist.
4. A pharmaceutical product according to claim 1 comprising two active ingredients which are a 5-HT₁ receptor agonist and a 5-HT re-uptake inhibitor.
5. A pharmaceutical product according to claim 1 comprising three active ingredients which are a 5-HT₃ receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT₁ receptor agonist.
6. A pharmaceutical product according to claim 1 wherein a 5-HT₃ receptor antagonist is selected from those described in WO 89/04660 and WO 90/01996.
7. A pharmaceutical product according to claim 1 wherein a 5-HT re-uptake inhibitor is selected from paroxetine, femoxetine, citalopram, sertraline, fluoxetine, clomipramine, fluvoxamine, cianopramine, ifoxetine, cericlamine, SL 810385 and seproxetine.

-9-

8. A pharmaceutical product according to claim 1 wherein the 5-HT₁ receptor agonist is sumatriptan.

9. A pharmaceutical composition comprising two or three active ingredients selected from a 5-HT₃ receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT₁ receptor agonist in combination with a pharmaceutically acceptable carrier.

10 10. The use of two or three active ingredients selected from a 5-HT₃ receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT₁ receptor agonist in the manufacture of a pharmaceutical preparation for simultaneous, separate or sequential use in depression and/or migraine therapy.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 A 61 K 45/06 A 61 K 31/445 A 61 K 31/415 // (A 61 K 31/445 A 61 K 31:415 A 61 K 31:40)		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO,A,8904660 (BEECHAM GROUP PLC) 1 June 1989, see the whole document (cited in the application) ---	1-10
A	Chemical Abstracts, vol. 113, no. 7, 13 August 1990, (Columbus, Ohio, US), A.J. Sleight et al.: "In vivo effects of sumatriptan (GR 43175) on extracellular levels of 5-HT in the guinea pig", see page 52, abstract 52433q, & Neuropharmacology 1990, 29(6), 511-13 ---	1-10
A	Chemical Abstracts, vol. 107, no. 23, 7 December 1987, (Columbus, Ohio, US), D.R. Thomas et al.: "Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxytryptamine uptake inhibitor", see pages 43,44, abstract 211787c, & Psychopharmacology (Berlin) 1987, 93(2), 193-200 -----	1-10
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
20-09-1991	17. 10. 91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 Mme. M. van der Drift	

GB 9100992
SA 48758

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8904660	01-06-89	AU-A- 2626488	14-06-89
		EP-A- 0340270	08-11-89
		JP-T- 2502185	19-07-90
<hr/>			

FTD KCRM 10079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82